

Low dose radiation therapy for the treatment of refractory canine osteoarthritis

Daniela B. Solis, Monique N. Mayer

Questions

1. Which of the following statements regarding low dose radiation therapy (LDRT) for osteoarthritis is *not* correct?
 - A. Pain relief is primarily due to the anti-inflammatory effects of ionizing radiation.
 - B. LDRT is recommended as an alternative to medical management for early osteoarthritis causing low grade lameness.
 - C. Studies of LDRT have shown improvement in pain and function for both human and canine osteoarthritis patients.
 - D. No early or late radiation side effects have been reported in dogs treated with LDRT.
2. Following a single low dose radiation therapy protocol using 3 fractions of 2 Gy in dogs with chronic osteoarthritis unresponsive to medical management, the reported median duration of clinical benefit was approximately:
 - A. 3 months
 - B. 6 months
 - C. 1 year
 - D. 2 years

(see page 872 for answers)

Osteoarthritis (OA) is a progressive clinical condition estimated to affect up to 20% of dogs > 1 year-of-age (1). It is associated with degradation of articular cartilage and is often accompanied by synovial inflammation, peri-articular osteophytosis, and alterations in subchondral bone metabolism. Osteoarthritis is a painful condition that negatively affects animal welfare and requires considerable, life-long clinical care (2). The pathological changes in the tissues of synovial joints associated with OA are irreversible; therefore, treatment is largely palliative and primarily centered around pain management and slowing disease progression.

Western College of Veterinary Medicine, 52 Campus Drive, University of Saskatchewan, Saskatoon, Saskatchewan S7N 5B4. Address all correspondence to Dr. Monique Mayer; email: monique.mayer@usask.ca

Use of this article is limited to a single copy for personal study. Anyone interested in obtaining reprints should contact the CVMA office (hbroughton@cvma-acmv.org) for additional copies or permission to use this material elsewhere.

Commonly used medical interventions include the use of analgesics, nutraceuticals, intra-articular agents, physical therapy, weight management, and alternative therapies such as acupuncture and physical rehabilitation: all of which have varying efficacies as measured through veterinarian/owner assessment, force platform analysis, or histological grading of cartilage structure and integrity (3). When conservative therapy with medical management is no longer adequate or effective, surgical interventions may be attempted to alleviate pain and return some joint function. Reported surgical interventions include total hip replacement with cemented implants, which has a 91 to 95.2% success rate (defined by satisfactory hip joint function), excision arthroplasty which has a 60 to 83% success rate (defined by slight or intermittent lameness), and partial synovectomy, which has a 75 to 80% success rate (defined by pain-free return to function) (4).

Ionizing radiation has long been a crucial therapeutic tool in human and companion animal oncology. In addition to its ability to target DNA and damage neoplastic cells, low doses of ionizing radiation have also been shown to have therapeutic effects in benign non-neoplastic conditions such as OA due to its immunomodulating and anti-inflammatory properties (5,6). Chronic low-grade inflammation plays an important role in the pathophysiology of OA and therefore is an important target in the therapeutic management of the condition (7). The proposed mechanisms by which low dose radiation therapy (LDRT) exerts its therapeutic effects include reduction of peripheral blood mononuclear cell adhesion, reduction of leukocyte adhesion by increasing anti-inflammatory cytokine TGF- β 1 expression, and attenuation of the expression of adhesion molecule E-selectin, which is responsible for the rolling motion of leukocytes on the endothelial surface during inflammation (5,6). Additional mechanisms include reduced production of nitric oxide, which is associated with increased vascular permeability and inflammatory pain and reduction of the release of reactive oxygen species by activated macrophages.

Low dose radiation therapy has shown clinical efficacy in the alleviation of pain associated with OA and improvement in joint function in human patients and is even considered standard treatment in some countries, such as Germany (8). Low dose radiation therapy has also shown efficacy in alleviating clinical symptoms in various laboratory animal models of arthritis (9). An intra-articular injection of a radionuclide that emits radiation locally significantly improved pain and function in 14 dogs with elbow OA; however, this commercial product is not available in Canada (10).

Two studies in dogs have shown encouraging evidence for the role of external beam radiation therapy in the treatment of OA, especially in those cases that are refractory to medical management. In one prospective study, a single-fraction 10 Gy protocol was performed on 5 Labrador retrievers with elbow OA unresponsive to medical treatment. This resulted in significant, although short-lived, improvements in weight-bearing of the affected limb (10). In a second retrospective study, 25 dogs with chronic unresponsive pain in ≥ 1 joints were followed for a median of 437 d after treatment with a radiation protocol of 3 fractions of 2 Gy delivered over 3 consecutive days or on alternating days (11). The dogs in this study had a mean age of 8.9 y and a mean weight of 33 kg and had been treated prior to radiation therapy using non-steroidal anti-inflammatory drugs, steroids, opiates, nutraceuticals, and/or physiotherapy. Forty percent of dogs were obese (BCS: 7-9/9) and 52% had a lameness score of 4/5. Ninety-two percent of dogs showed either a partial response (defined as an improvement in lameness score of at least one grade) or a complete response (defined as complete resolution of lameness). This clinical benefit lasted a median of 356 d with 22 out of 24 owners expressing satisfaction with the improvement in their dog's quality of life. Four dogs were re-treated with the same protocol at the time of symptom recurrence and clinical improvements were once again observed and lasted for a median of 418 d. Forty-eight percent of dogs received no medical therapy after radiation treatment, and no acute or late side effects were observed in dogs that received either one or multiple courses of LDRT. Preliminary data from these studies provide support for the use of LDRT in the management of refractory canine OA.

Veterinarians can refer clients for consultation to determine if radiation therapy is an appropriate treatment option for specific cases of osteoarthritis. Eligible cases include dogs with visible evidence of OA on radiographs and clinical signs of pain and/or lameness which is no longer controlled by other appropriate treatments. Because the radiation treatment is administered under short general anesthesia, a CBC, serum biochemistry, and urinalysis performed by a laboratory within the last 2 wk and thoracic radiographs are required. Radiographs of the affected joint or joints are used to plan radiation treatment fields. Treatment at the Western College of Veterinary Medicine consists of a protocol of 2 Gy administered daily for 3 d on an outpatient basis using a linear accelerator. No acute or late side effects of radiation treatment were noted in the preliminary studies described above; however, some animals may experience mild fatigue, gastrointestinal signs, or a decrease in appetite following treatment, related to the stress of hospitalization and general anesthesia.

In conclusion, LDRT is a safe treatment option, performed on an outpatient basis, that shows promise for improving the quality of life of dogs with refractory canine OA.

Answers

1. B. LDRT is recommended as an alternative to medical management for early osteoarthritis causing low grade lameness.

At this time, LDRT has been used for patients with OA that is refractory to medical management. Low dose ionizing radiation targets inflammation associated with osteoarthritis, and this is a mechanism for the relief of pain reported in both human and canine patients. Early side effects of radiation therapy would not be expected at the radiation doses used for treating osteoarthritis. Although there is no dose threshold for late radiation side effects, the risk would be very low at the doses delivered for osteoarthritis and no late effects have been reported in veterinary patients.

2. C. 1 year. A median duration of 356 days of clinical improvement was reported by Italian researchers in 2018 (12).

References

1. Johnston SA. Osteoarthritis — Joint anatomy, physiology, and pathobiology. *Vet Clin North Am Small Anim Pract* 1997;27:699–723.
2. Summers JE, O'Neill DG, Church D, Collins L, Sargan D, Brodbelt DC. Health-related welfare prioritisation of canine disorders using electronic health records in primary care practice in the UK. *BMC Vet Res* 2019;15:163.
3. Sanderson RO, Beata C, Flipo RM, *et al.* Systematic review of the management of canine osteoarthritis. *Vet Rec* 2009;164:418–424.
4. Cook JL, Payne JT. Surgical treatment of osteoarthritis. *Vet Clin North Am Small Anim Pract* 1997;27:931–944.
5. Rödel F, Frey B, Manda K, *et al.* Immunomodulatory properties and molecular effects in inflammatory diseases of low-dose x-irradiation. *Front Oncol* 2012;2:120.
6. Rödel F, Keilholz L, Herrmann M, Sauer R, Hildebrandt G. Radiobiological mechanisms in inflammatory diseases of low-dose radiation therapy. *Int J Radiat Biol* 2007;83:357–366.
7. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: Latest findings and interpretations. *Ther Adv Musculoskelet Dis* 2013;5:77–94.
8. Javadinia SA, Nazeminezhad N, Ghahramani-Asl R, *et al.* Low-dose radiation therapy for osteoarthritis and enthesopathies: A review of current data. *Int J Radiat Biol* 2021;97:1352–1367.
9. Calabrese EJ, Calabrese V. Low dose radiation therapy (LD-RT) is effective in the treatment of arthritis: Animal model findings. *Int J Radiat Biol* 2013;89:287–294.
10. Donecker J, Fabiani M, Gaschen L, Aulakh KS. Treatment response in dogs with naturally occurring grade 3 elbow osteoarthritis following intra-articular injection of 117 mSn (tin) colloid. *PLoS One* 2021;16:e0254613.
11. Kapatkin AS, Nordquist B, Garcia TC, *et al.* Effect of single dose radiation therapy on weight-bearing lameness in dogs with elbow osteoarthritis. *Vet Comp Orthop Traumatol* 2016;29:338–343.
12. Rossi F, Cancedda S, Leone VF, Bley CR, Laganga P. Megavoltage radiotherapy for the treatment of degenerative joint disease in dogs: Results of a preliminary experience in an Italian radiotherapy centre. *Front Vet Sci* 2018;5:74.